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| 10/552,836 | 10/13/2005 | Michael Forstner | TX/4-33176A | 2236 |

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ONE HEALTH PLAZA 104/3
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| EXAMINER | |
|---|---|
| WEN, SHARON X | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/552,836 | FORSTNER ET AL. | |
| | Examiner | Art Unit | |
| | Sharon Wen | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 3-10* is/are pending in the application.

4a) Of the above claim(s) *1,3 and 5-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicant's amendment, filed 10/13/2005, has been entered.

Claim 2 has been canceled.

Claims 1 and 3-10 are pending.

### *Election/Restrictions*

2. Applicant's election without traverse of Group II drawn to an inhibitor of a Vav protein, a therapeutic combination and a pharmaceutical composition comprising an inhibitor of a Vav protein in the replies filed on 07/26/2007 is acknowledged.

Applicant's subsequence election of species of the inhibitor of Vav drawn to an anti-Vav1 antibody in the replies filed on 09/26/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the species election requirement, the species election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1, 3 and 5-8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention, there being no allowable generic or linking claim.

Claims 4 and 9-10 are currently under examination as they read on an inhibitor of a Vav protein, a therapeutic combination and a pharmaceutical composition comprising an inhibitor of a Vav protein, wherein the elected inhibitor is an anti-Vav1 antibody.

### *Priority*

3. The effective domestic priority date for claims 4 and 9-10 is deemed the effective filing date of PCT/EP04/03982, i.e., 04/15/2004.

Applicant's claim for foreign priority is acknowledged. Certified copies of foreign priority applications, 0308853.1 and 0315090.1, submitted under 35 U.S.C. 119(a)-(d), have been placed of record in the file. The foreign priority applications appear to have support for claims 4 and 9-10.

Applicant is invited to amend the first line of the specification to reflect Applicant's claim for priority.

### *Information Disclosure Statement*

4. The information disclosure statements (IDS) submitted on 10/13/2005 and 05/18/2006 is acknowledged and being considered by the examiner.

### *Specification*

5. Applicant is requested to review the application for any spelling error, use of trademarks, embedded hyperlinks and/or other form of browser-executable code.

Trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Embedded hyperlinks and/or other form of browser-executable code are impermissible in the text of the application as they represent an improper incorporation by reference.

### *Claim Objections*

6. Claims 9-10 are objected to because of the following informalities:

The instant claims depend from non-elected claims.

Further, it is noted the claim 6 requires the essential steps recited in claim 5.

For the purpose of examination, claim 9 reads on a screening method according to the steps recited in claims 5 and 6. Similarly, claim 10 reads on "a method as defined in claim 1".

Applicant is required to amend the claims to recited the limitations from non-elected claims.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) The instant claim is indefinite for being in improper Markush format. The Office recommends the use of the phrase "**selected from the group consisting of**..." with the use of the conjunction "**and**" rather than "or" in listing the species. See MPEP 2173.05(h).

Currently, there appears to be missing the word "and" between "drug" and "a chemotherapeutic agent".

B) It is also noted that the term "therapeutic combination" recited in claim 4 is interpreted to read on "a kit" (see page 22 of the specification), while the accepted meaning is "a composition." The term is indefinite because the specification does not clearly redefine the term.

For the purpose of examination, the term "therapeutic combination" reads on a "therapeutic composition".

C) Applicant is reminded that any amendment must point to a basis in the specification so as not to add New Matter. See MPEP 714.03 and 2163.06.

***Claim Rejections - 35 USC § 112***

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 4 and 9-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is insufficient written description of the genus encompassed by the recitation of "a Vav protein" and "an active fragment or mutant thereof".

There is insufficient written description of the claimed genus of "Vav proteins" or "active fragments or mutants thereof" in the absence of defining the relevant identifying characteristics such as the structure of other physical and/or chemical characteristics of the claimed genus.

The instant specification describes the "Vav protein" to include Vav1, Vav2, and Vav3 (see page 1 of specification).

The specification as filed does not provide written description for "Vav proteins or active fragments or mutants thereof", broadly commensurate in scope with the claimed invention.

There is insufficient written description to lead a person of skill in the art to know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences for identifying "Vav proteins" indicated above and disclosed in the specification as filed.

A person of skill in the art was not in possession of the breadth of claimed "Vav proteins or active fragments or mutants thereof" because it was well known in the art at the time the invention was made that molecules with sequence similarity often have different functions.

For example, Attwood (Science 290: 471-473, 2000) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences.

Similarly, Skolnick et al. (Trends in Biotech. 18: 34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C § 112, paragraph 1 "Written Description" requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January, 2001, See especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.) Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision. (See page 1115.)

11. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

With regards to the instant claims, their breadth, the state of the prior art, and the lack of guidance provided by the inventor, comprise the primary issues as regards the unpredictability of the claimed method.

Claims 10 is directed to a pharmaceutical composition comprising a Vav inhibitor for preventing or treating (i) acute or chronic graft rejection in a recipient of cell, tissue or organ allo- or xenotransplant, (ii) an inflammatory or autoimmune disease in a subject in need thereof, (iii) vein graft stenosis, restenosis and/or vascular occlusion following vascular injury or (iv) a malignant proliferation disease in a subject in need thereof. However, the specification does not enable one of skill in the art at the time the invention was made to use the pharmaceutical composition for preventing the various disease broadly encompassed by the claims.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The specification does not adequately teach how to effectively prevent any disease or reach an appropriate beneficial therapeutic endpoint in humans by administering an inhibitor of Vav, in particular, an anti-Vav1 antibody. The specification does not teach how to extrapolate data obtained from various in vitro or in vivo observations with the pharmaceutical composition comprising Vav inhibitor to the development of effective methods of preventing human diseases broadly encompassed by the claimed invention and consistent with the disclosure of various diseases and disorders disclosed on pages 12-14 of the instant specification.

According to *The Merck Manual of Diagnosis and Therapy*, the precise causes of rheumatoid arthritis, a species of autoimmune and inflammatory disease disclosed in the instant specification (see page 13 of the specification), is unknown. While many factors, such as smoking or viral infections, are thought to play a role, a genetic predisposition has been identified in a certain population to contribute to the chronic autoimmune manifestation (*The Merck Manuals Online Medical Library,* [online]. Whitehouse Station, NJ: Merck Research Laboratories, 2006-2007. [retrieved on 10/09/2007]. Retrieved from the Internet: < URL: http://www.merck.com/mmpe/print/sec04/ch034/ch034b.html>. Rheumatoid Arthritis (RA), see pages 1-9). However, the instant disclosure does not provide sufficient in vitro or in vivo evidence showing the administration of a pharmaceutical composition comprising a Vav inhibitor can counter-act the cause or the manifestation of rheumatoid arthritis as defined by *The Merck Manual of Diagnosis and Therapy* in order to prevent the disease.

Also, it is noted that experimental protocols usually are conducted under defined conditions wherein the antagonist and the stimulus / insult occur at the same or nearly the same time. Cytokine inhibition is much easier to achieve under such controlled conditions than that experienced in the human disorders or diseases such as rheumatoid arthritis targeted by the claimed invention (see pages 12-14 of the instant specification).

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective methods to prevent the scope of various diseases disclosed and in view of lack of sufficient working examples provided by Applicant of using a Vav inhibitor, undue experimentation would be required to practice the claimed methods of preventing diseases with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for preventing the diseases or disorders encompassed by the claimed methods.

With respect to "preventing", Applicant is invited to amend the claims to avoid the recitation of "preventing".

***Claim Rejections - 35 USC § 102***

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Piccolella et al. (*Journal of Immunology*, 2003, 170:2895-1903, see entire document).

Piccolella et al. teach a Vav inhibitor wherein the Vav inhibitor is an anti-Vav1 antibody (see page 2896, left column, **Materials and Methods**, *Cell lines, Abs, and reagents*).

It is noted that the claim 9 provides product-by-process limitations in the recitation of "obtainable by a screening method according to claim 6." Given the reference teach an anti-Vav1 antibody, the same protein could also be obtainable by a screening method according to claim 6.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

***Claim Rejections - 35 USC § 103***

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 4 and 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hilton et al. (US Patent 6,323,317) in view of Sepulveda et al. (The Journal of Biological Chemistry 2000, 275:14005-14008).

Hilton et al. teach a Vav-1 inhibitor named SOCS-1, as evidenced by Sepulveda (see entire documents for both Hilton et al. and Sepulveda et al., in particular, see Summary of the Invention for Hilton et al. and title for Sepulveda et al.).

In addition, Hilton et al. teach a pharmaceutical composition comprising the Vav-1 inhibitor and a pharmaceutically acceptable diluent or carrier (see column 30, first full paragraph).

Moreover, Hilton et al. teach a therapeutic combination comprising the Vav-1 inhibitor and a second agent that is an antibacterial or antifungal agent which reads on a chemotherapeutic agent (see column 30, second full paragraph, in particular, line 30).

Hilton et al. do not teach an anti-Vav-1 antibody. However anti-Vav-1 antibodies are well known in the art at the time of the invention as demonstrated by Sepulveda et al. (see page 14005, right column, last full paragraph).

Therefore, it would have been prima facie obvious to substitute SOCS-1 as a Vav-inhibitor in a therapeutic combination or pharmaceutical composition as taught by Hilton et al. for an anti-Vav-1 antibody as taught by Sepulveda et al..

One of ordinary skill in the art would have been motivated to combine the anti-Vav-1 antibody in the pharmaceutical composition or therapeutic combination because Hilton et al. teach that the Vav-1 inhibitor is useful in modulating cellular responsiveness to cytokines as well as other mediators of signal transduction such as endogenous or exogenous molecules, microbial products, viruses or parasites (see Abstract).

Therefore, the invention, as a whole, was *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made as evidenced by the references, especially in the absence of evidence to the contrary.

***Conclusion***

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon Wen whose telephone number is (571) 270-3064. The examiner can normally be reached on Monday-Thursday, 8:30AM-6:00PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sharon Wen, Ph.D.
Patent Examiner
October 12, 2007

PHILLIP GAMBEL, PH.D JD
PRIMARY EXAMINER
TC 1600
10/13/07